Claim Terms "At Least A Portion" and "In Common"

In an Advisory Action, dated April 10, 2003, the Examiner suggested the claim amendments filed March 11, 2003, and particularly the claim terms, "at least a portion" and "in common" raise new issues and possibly new matter. Applicants submit the terms , "at least a portion" and "in common" are supported by the specification and thus do not constitute new matter. Support for both terms is found on page 2, lines 1-5 and 11-20; page 10, line 10-page 11, line 1; page 14, lines 10-22.

The Use of Computer Programs

In an Advisory Action, dated April 10, 2003, the Examiner indicated Applicants had not addressed the use of computer programs in the design of humanized antibodies. The Examiner referred to the programs ABMOD and ENCODE in the Office Action dated December 30, 2002 in discussing the obviousness rejection. The Examiner correctly quotes from the specification in the office action:

> The computer programs ABMOD and ENCODE (Levitt et al. 1983, J. Mol. Biol. 168:595) were used to construct a molecular model of the 3D1 variable domain, which was used to locate the amino acids in the 3D1 framework that are close enough to the CDRs to potentially interact with them. To design the humanized 3D1 heavy and light chain variable regions, the CDRs from the mouse 3D1 heavy chain were grafted into the framework regions of the human III2R heavy chain and the CDRs from the mouse 3D1 light chain grafted into the framework regions of the human H2F light chain. At framework positions where the computer model suggested significant contact with the CDRs, the amino acids from the mouse antibody were substituted for the original human framework residues.

(page 36, lines 1-10).

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

The use of the computer programs ABMOD and ENCODE do not make the claimed invention obvious. Applicants had previously argued that the Office failed to establish a prima facie case of obviousness because the cited references did not teach or suggest the use of the III2R and H2F human antibodies and even if the a skilled artisan had been aware of these antibodies, there would have been no reasonable expectation of success in attaining the claimed invention because no cited reference demonstrated that homology existed between the 3D1 and III2R and H2F antibodies. The specification discloses the importance of homology between the human and murine antibodies:

> The choice of framework residues can be critical in retaining high binding affinity. In principle, a framework sequence from any human antibody can serve as the template for CDR grafting; however, it has been demonstrated that straight CDR replacement into such a framework can lead to significant loss of binding affinity (Tempest et al. *Biotechnology* 9:266 (1992); Shalaby et al. *J. Exp. Med.* 17:217 (1992)). The more homologous a human antibody is to the original murine antibody, the less likely the human framework will introduce distortions into the mouse CDRs that could reduce affinity. Based on a sequence homology, III2R was selected to provide the framework for the humanized 3D1 heavy chain and H2F for the humanized 3D1 light chain variable region.

(page 35, lines 4-13)

The computer programs ABMOD and ENCODE were not used to select these homologous antibodies, but rather to merely construct computer based structural models of the three antibodies to determine which residues in the framework region should not be humanized, i.e., be derived from the murine antibody, 3D1. The computer programs were used <u>after</u> the selection of the murine 3D1 antibody and the

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

human H2F and III2R antibodies was made. It is the Applicants' position that the Office has not cited a reference that discloses humanizing the 3D1 antibody with the H2F and III2R antibodies would be either desirable or reasonably successful. The use of the programs ABMOD and ENCODE does nothing to change that fact.

Lastly, the Examiner raises concerns in the Advisory Action regarding the teaching in the specification that the humanized FR will possess 60%, preferably 80% overall sequence identity with the variable region of the nonhuman donor. Applicants submit that this does not render the claimed subject matter obvious. Again, nothing in any of the references cited by the Office teaches the framework regions of the III2R or H2F antibodies would be reasonably successful in humanizing the 3D1 antibody and nothing in any cited reference suggests that any homology existed between 3D1 and either III2R or H2F antibodies. Accordingly, the Office has not established a prima facie case of obviousness and Applicants respectfully request the rejection be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request the reconsideration and re-examination of this Application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Customer No. 22,852
Application No. 09/627,896
Attorney Docket No. 08702.0081-01000

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 26, 2003

By: E Stewart Mittler
E. Stewart Mittler
Reg. No. 50,316

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com